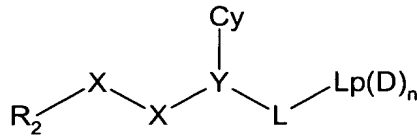


Clean Set of Claims

1. A serine protease inhibitor compound of formula (I)



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(I)

wherein:

R<sub>2</sub> is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, MeSO<sub>2</sub>- or R<sub>1</sub>, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxy, carbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R<sub>2</sub> cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR<sub>1a</sub>, C(R<sub>1a</sub>)<sub>2</sub> or NR<sub>1a</sub> group, at least one X being C, CO, CR<sub>1a</sub> or C(R<sub>1a</sub>)<sub>2</sub>;

each R<sub>1a</sub> independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxy, carbonyl, alkylaminocarbonyl, alkoxy, carbonyl, amino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R<sub>1</sub> is as defined for R<sub>1a</sub>, provided that R<sub>1</sub> is not unsubstituted aminoalkyl;

Y (the α-atom) is a nitrogen atom or a CR<sub>1b</sub> group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups

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~~R<sub>3a</sub> or R<sub>3i</sub>X<sub>i</sub>;~~

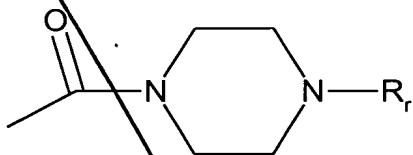
~~each R<sub>3a</sub> independently is R<sub>1c</sub>, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkylloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula -C(X<sup>3</sup>)N(R<sup>11</sup>)R<sup>12</sup> (wherein X<sup>3</sup> is O or S; and R<sup>11</sup> and R<sup>12</sup> are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or -OCH<sub>2</sub>O- which is bonded to two adjacent ring atoms in Cy;~~

~~X<sub>i</sub> is a bond, O, NH or CH<sub>2</sub>;~~

~~R<sub>3i</sub> is phenyl, pyridyl or pyrimidinyl optionally substituted by R<sub>3a</sub>;~~

~~R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1j</sub> are as defined for R<sub>1a</sub>; and~~

~~-L-Lp(D)<sub>n</sub> is of the formula:~~



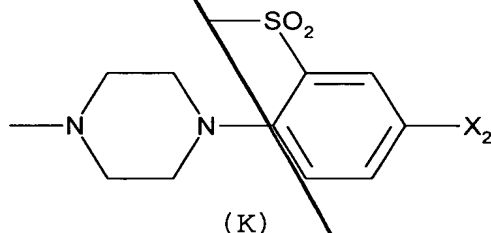
~~in which R<sub>f</sub> is -(CH<sub>2</sub>)<sub>c</sub>-R<sub>c</sub>, -CHR<sub>e</sub>R<sub>f</sub>, -CH<sub>2</sub>-CHR<sub>e</sub>R<sub>f</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-CHR<sub>e</sub>R<sub>f</sub>, or R<sub>g</sub> in which c is 1 or 2; R<sub>c</sub> is thienyl, thiazolyl (which may bear an amino substituent), isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridyl (which may bear an alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, (1-4C)alkoxycarbonyl, carboxy, acetyl amino, chloro, fluoro, cyano, (1-3C)alkyl, trifluoromethyl, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl or tetrazolyl substituent), pyrimidinyl, pyridazinyl, pyrazinyl or phenyl (which may bear a methyl, methylamino, dimethylamino, carboxy, dialkylaminosulphonyl, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxycarbonyl, acetyl amino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl or tetrazolyl substituent); each of R<sub>e</sub> and R<sub>f</sub> independently is hydrogen or C<sub>1-3</sub>alkyl; or CHR<sub>e</sub>R<sub>f</sub> is cyclopentyl (which may~~

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- 3 -

bear a hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl substituent at the 3- or 4-position), cyclohexyl (which may bear a hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl substituent at the 3- or 4-position), tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, pyrrolidin-3-yl (which may bear a hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl substituent at the 1-position), piperidin-4-yl (which may bear a hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl substituent at the 1-position), or indan-2-yl; and  $R_g$  is 2-methylsulphonylphenyl which may bear a 4-fluoro substituent or  $R_g$  is  $\lambda^6$ -1,1-dioxobenzo[b]thiophen-7-yl;

or a physiologically-tolerable salt thereof;  
provided that  $Lp(D)_n$  is not of the formula (K):



wherein  $X_2$  is fluoro or hydrogen.

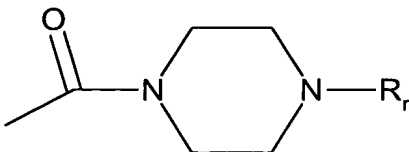
2. (amended) A compound according to claim 1  
wherein

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups  $R_{3a}$  or phenyl optionally substituted by  $R_{3a}$ ;

each  $R_{3a}$  independently is  $R_{1c}$ , amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl; and

-L- $Lp(D)_n$  is of the formula:

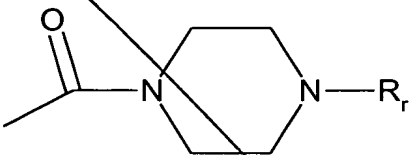
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in which  $R_f$  is  $-(CH_2)_c-R_c$ ,  $-CH(R_e)R_f$ ,  $-CH_2-CH(R_e)R_f$ , or  $R_g$  in which  $c$  is 1 or 2;  $R_c$  is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl,  $CONH_2$ ,  $SO_2NH_2$ ,

- 5 methylaminosulphonyl, dimethylaminosulphonyl, methoxy or methylsulphonyl substituent); each of  $R_e$  and  $R_f$  independently is hydrogen or  $C_{1-3}$ alkyl; or  $CH(R_e)R_f$  is cyclopentyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position), cyclohexyl (which may bear a methyl, ethyl or
- 10 hydroxymethyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl substituent at the 3- or 4-position), tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, pyrrolidin-3-yl (which may bear a 1-methyl substituent), piperidin-4-yl (which may bear a 1-methyl substituent), or indan-2-yl; and  $R_g$
- 15 is 2-methylsulphonylphenyl which may bear a 4-fluoro substituent or  $R_g$  is  $\lambda^6$ -1,1-dioxobenzo[b]thiophen-7-yl.

3. A compound according to claim 1 wherein  $-L-L_p(D)_n$  is of the formula:



20

- in which  $R_f$  is  $-(CH_2)_c-R_c$ ; in which  $c$  is 2;  $R_c$  is thienyl, thiazolyl (which may bear an amino substituent), isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridyl (which may bear an amino, methoxycarbonyl, carboxy,
- 25 fluoro, cyano, methyl, methylsulphonyl, aminosulphonyl, methylaminosulfonyl, dimethylaminosulfonyl, or trifluoromethyl substituent), pyrimidinyl, pyridazinyl, pyrazinyl or phenyl (which phenyl may bear a fluoro, chloro, cyano, methyl, amino, methylsulphonyl, aminosulphonyl, methylaminosulphonyl,
- 30 dimethylaminosulphonyl, methylamino, dimethylamino, carboxy, methoxycarbonyl or methoxy substituent).

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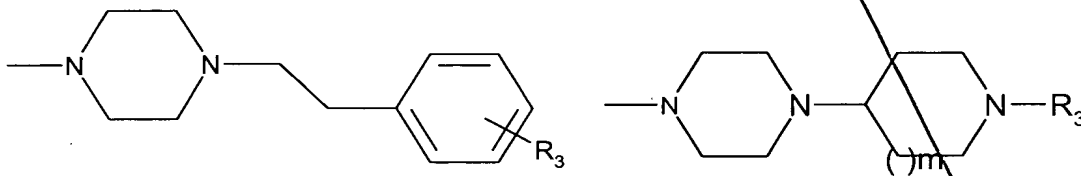
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4. (amended) A compound according to claim 3 wherein R<sub>c</sub> is thiazolyl (which may bear an amino substituent), pyrimidinyl, pyrazolyl, imidazolyl, pyridyl (which may bear a methylsulphonyl, aminosulphonyl, methylaminosulfonyl, dimethylaminosulfonyl, fluoro, cyano, methyl or trifluoromethyl substituent), pyridazinyl, pyrazinyl or phenyl (which phenyl may bear a fluoro, chloro, cyano, methyl, amino, methylamino, dimethylamino, carboxy, methoxycarbonyl, methylsulphonyl, aminosulphonyl, methylaminosulfonyl, dimethylaminosulfonyl, or methoxy substituent).

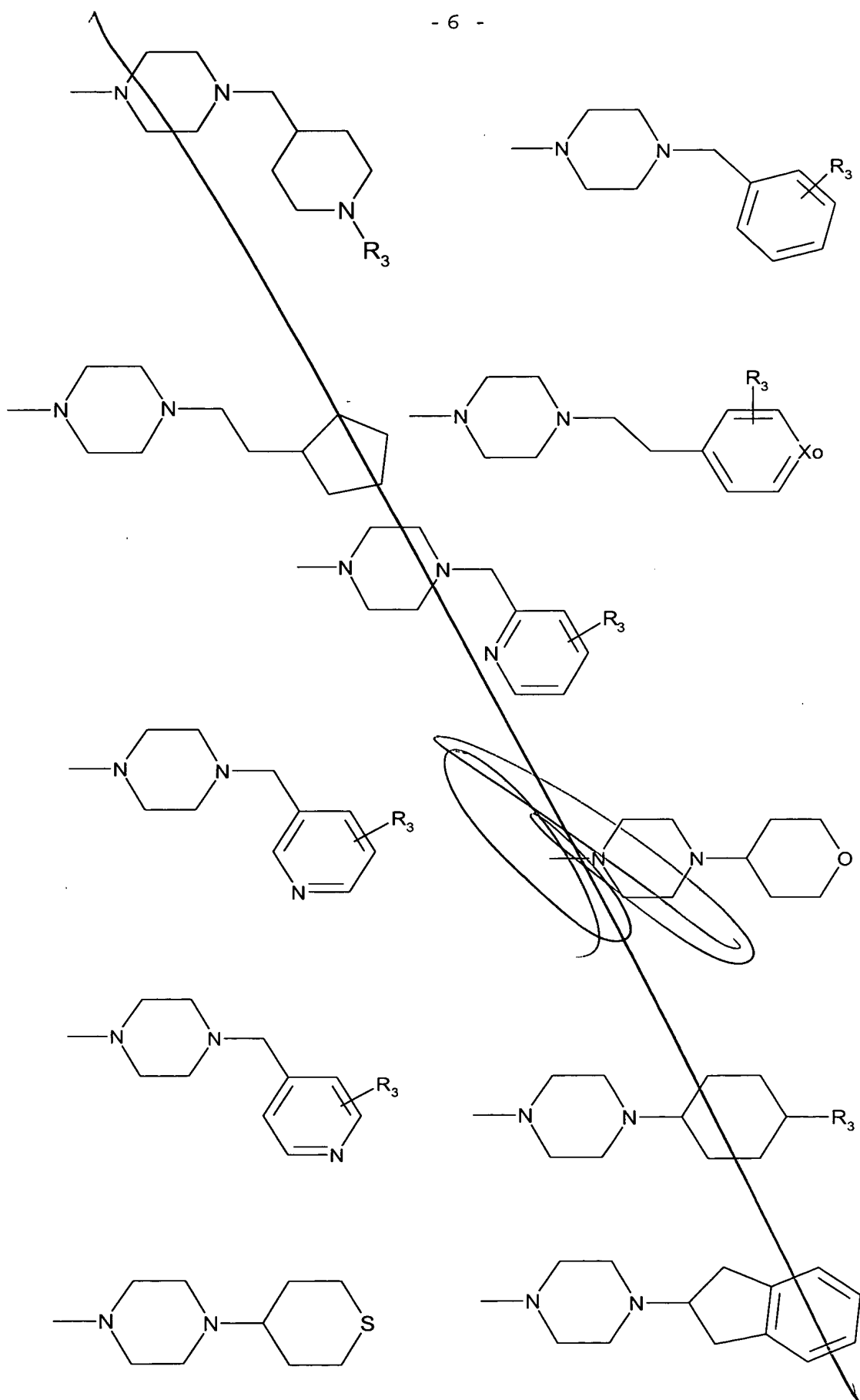
5. (amended) A compound according to claim 4 wherein R<sub>c</sub> is thiazolyl (which may bear an amino substituent), pyrazolyl, imidazolyl, pyridyl (which may bear a fluoro, cyano, methyl or trifluoromethyl substituent), pyridazinyl or pyrazinyl.

6. (amended) A compound according to claim 5 wherein R<sub>c</sub> is thiazol-2-yl, 2-aminothiazol-4-yl, pyrazol-1-yl, pyrazol-4-yl, pyridazin-3-yl, imidazol-1-yl, imidazol-4-yl, pyrazin-2-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 3-fluoropyrid-4-yl, 2-cyanopyrid-4-yl, 2-methylpyrid-4-yl or 2-trifluoromethylpyrid-6-yl.

7. (amended) A compound according to claim 1 wherein L is CO and -Lp(D)<sub>n</sub> is of the formula:



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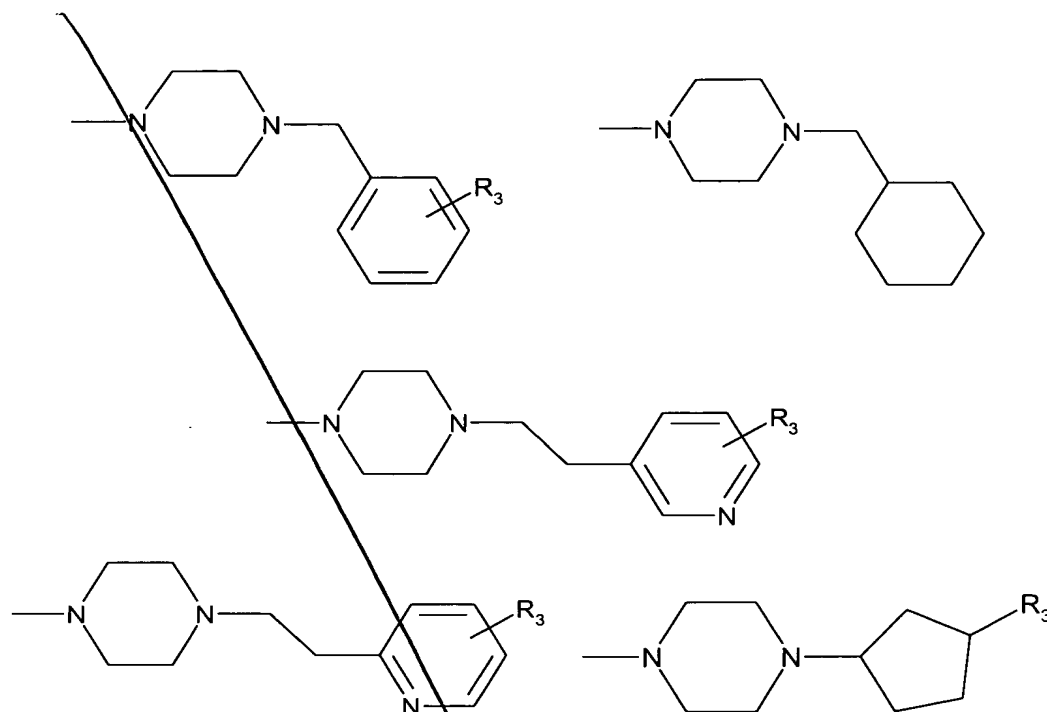
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*a<sup>3</sup>*

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wherein;

m represents 0 or 1;

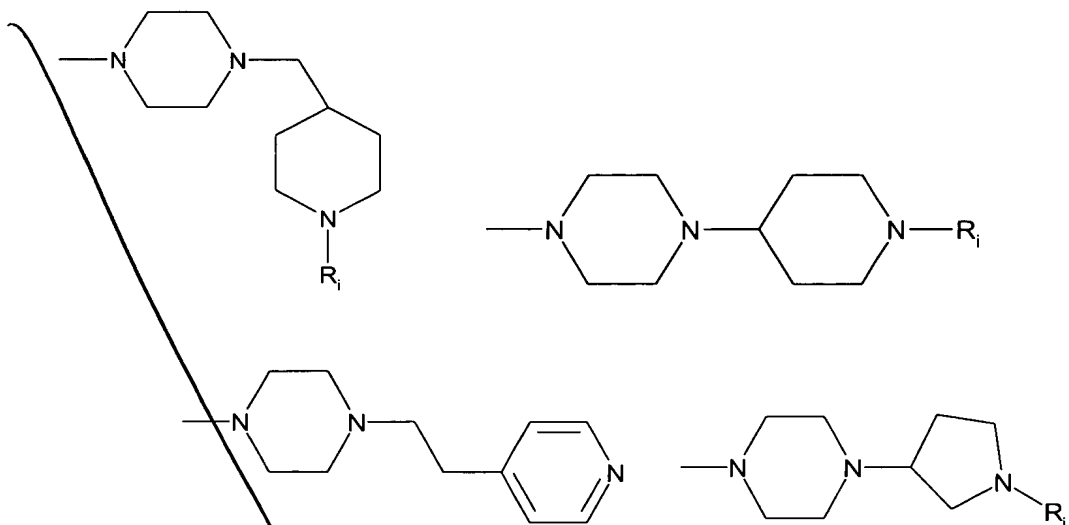
X<sup>0</sup> represents CH or N; and

when R<sub>3</sub> is present as a substituent on an aromatic ring, it is selected from hydrogen, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxy, acetyl, amino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl and tetrazolyl; and

when R<sub>3</sub> is present as a substituent on a saturated ring, it is selected from hydrogen, hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl and ethoxycarbonyl.

8. A compound according to claim 7 wherein -Lp(D)<sub>n</sub> is of the formula:

- 8 -



wherein  $R_1$  is hydrogen or (1-6C)alkyl.

5

9. (amended) A compound according to claim 1 wherein  $R_2$  is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl, benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl (each of which is optionally substituted as defined in claim 1).

10

10. (amended) A compound according to claim 9 wherein optional substituents for  $R_2$  are selected from:

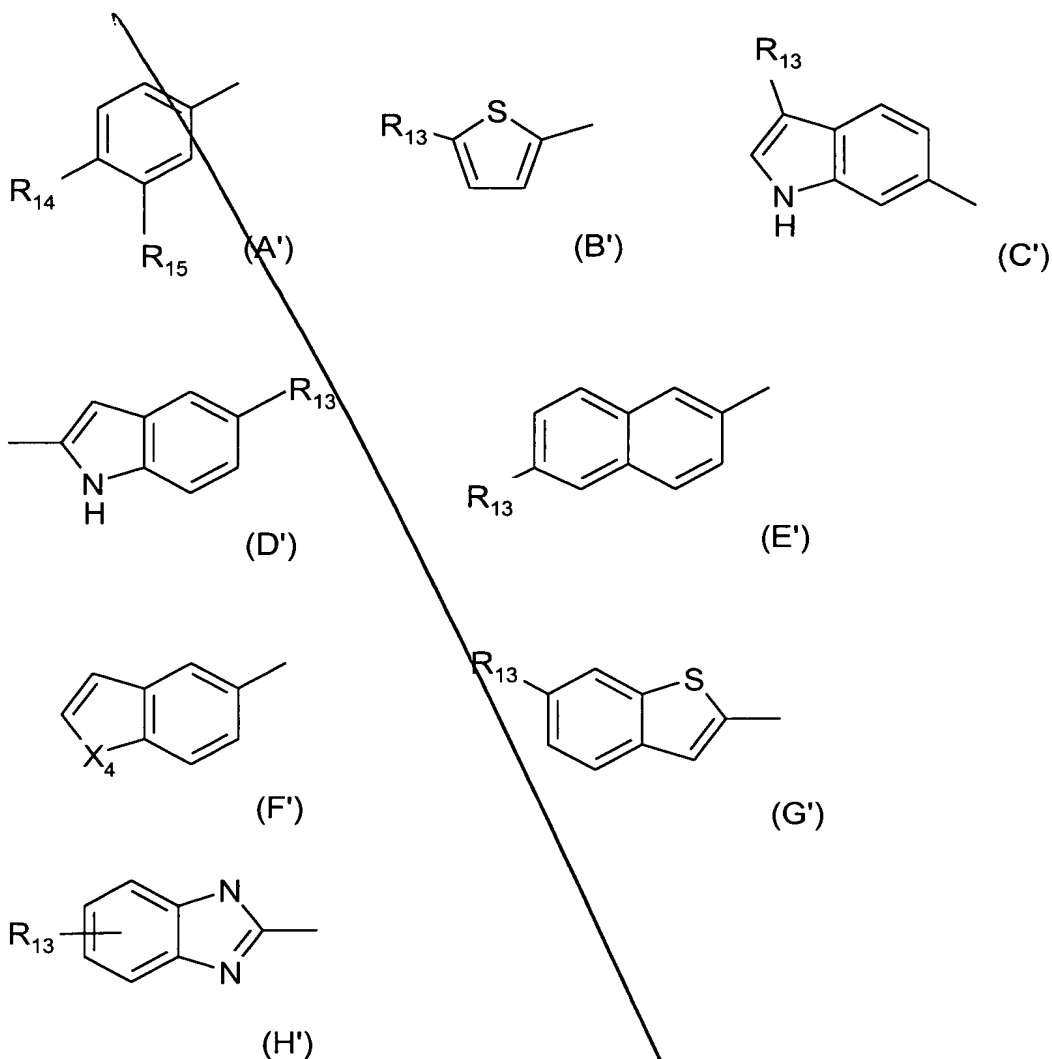
fluoro, chloro, bromo, iodo, nitro, thiol, difluoromethoxy, trifluoromethoxy, hydrazido, methylhydrazido, amino, cyano, trifluoromethyl, methylthio, vinyl, ethynyl, acetylamino, carboxy, acetoxy, hydroxy, methyl, ethyl, amido ( $\text{CONH}_2$ ), aminomethyl, methoxy and ethoxy.

11. (amended) A compound according to claim 1 wherein  $R_2$  is selected from one of the formula (A') to (H'):

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wherein X<sub>4</sub> is O or S, R<sub>13</sub> is selected from hydrogen, fluoro, [except for (C')] chloro or methyl and R<sub>14</sub> is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R<sub>15</sub> is selected from hydrogen, methyl, fluoro, chloro and amino.

12. (amended) A compound according to claim 11, wherein R<sub>2</sub> is 4-chlorophenyl, 4-methoxyphenyl, 3-amino-4-chlorophenyl, indol-2-yl, 5-chloroindol-2-yl, indol-6-yl, 3-chloroindol-6-yl or 3-methylindol-6-yl.

13. (amended) A compound according to claim 1 wherein -X-X- is -CONH-.

- 10 -

14. (amended) A compound according to any one of claims 1 to 13, 15 to 16 and 19 to 22 wherein Y is CH.

15. (amended) A compound according to claim 1 wherein Cy is an optionally R<sub>3a</sub> substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinolyl, isoquinolyl, benzofuryl, benzothienyl or cycloalkyl group, or a phenyl group substituted by R<sub>3i</sub>X<sub>i</sub> in which X<sub>i</sub> is a bond, O, NH or CH<sub>2</sub> and R<sub>3i</sub> is phenyl, pyridyl or pyrimidyl optionally substituted by R<sub>3a</sub>.

16. (amended) A compound according to claim 2 wherein Cy is an optionally R<sub>3a</sub> substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl or cycloalkyl group.

17. (cancelled on national phase entry)

18. (cancelled on national phase entry)

19. (amended) A compound according to claim 15 wherein R<sub>3a</sub> is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylamino-carbonyl, aminomethyl, CONH<sub>2</sub>, CH<sub>2</sub>CONH<sub>2</sub>, acetyl amino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, bromo, -OCH<sub>2</sub>O- (which is bonded to two adjacent ring atoms in Cy) and -C(X<sup>3</sup>)N(R<sup>11</sup>)R<sup>12</sup> (wherein X<sup>3</sup> is O or S and R<sup>11</sup> and R<sup>12</sup> are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group).

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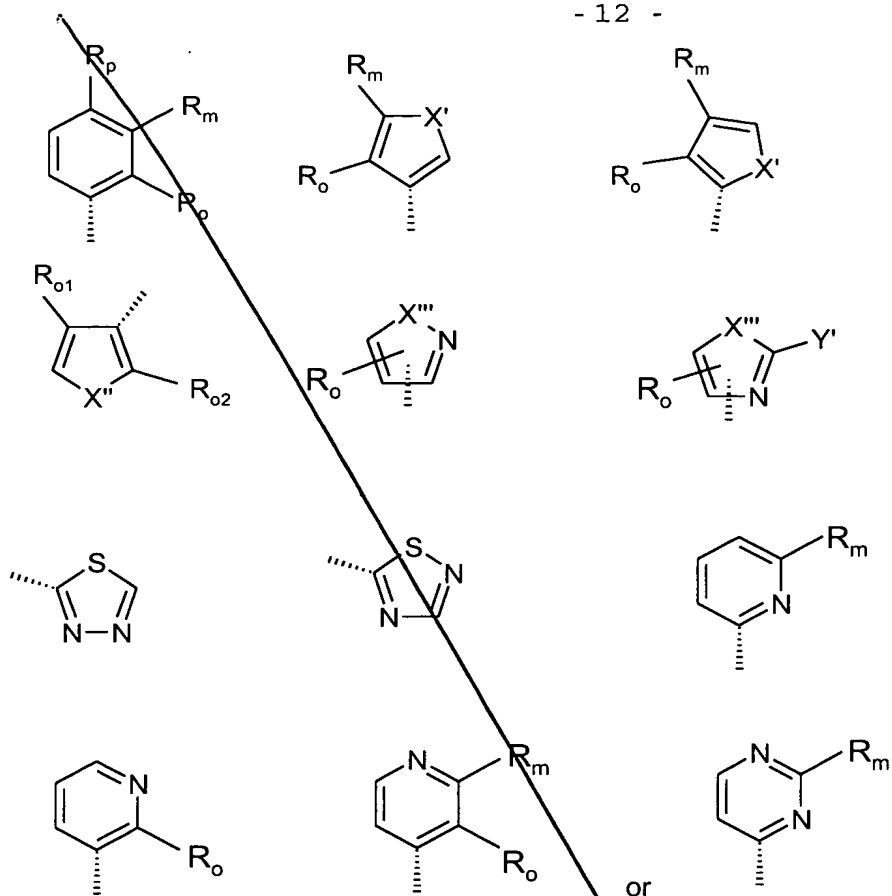
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20. (amended) A compound according to claim 16 wherein R<sub>3a</sub> is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, 5 carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylamino-carbonyl, aminomethyl, CONH<sub>2</sub>, CH<sub>2</sub>CONH<sub>2</sub>, acetyl amino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, 10 ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl.
- 15 21. (amended) A compound according to claim 1 wherein Cy is selected from:

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- 12 -



wherein:

X' is selected from O, S and NMe;

5 X'' is selected from O and S;

X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

10  $R_o$  is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphanyl and methylsulphonyl;

$R_m$  is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphanyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula  $-C(X^3)N(R^{11})R^{12}$  (wherein  $X^3$  is O or S and  $R^{11}$  and  $R^{12}$  are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);

$R_p$  is selected from hydrogen and fluoro; or

$R_o$  and  $R_m$  or  $R_m$  and  $R_p$  form an  $-OCH_2O-$  group; or

20  $R_o$  and  $R_m$  together with the ring to which they are attached

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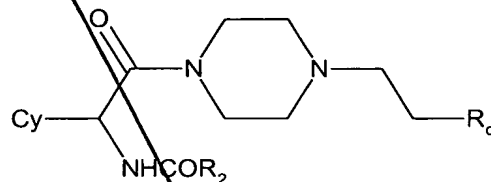
form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroaryl ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur);

one of  $R_{O1}$  and  $R_{O2}$  is hydrogen and the other is  $R_O$ ;

5

22. (amended) A compound according to claim 1 wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, 10 thiazol-4-yl, thiazol-5-yl and quinolin-4-yl.

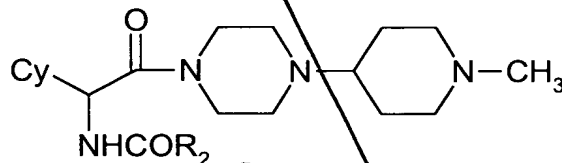
23. (amended) A compound of the formula:



wherein Cy,  $R_2$  and  $R_C$  are as defined in claim 1.

15

24. (amended) A compound of the formula:



wherein Cy and  $R_2$  are as defined in claim 1.

20

25. (amended) A compound as claimed in Claim 14, in which the alpha atom in Y is carbon and has the conformation that would result from construction from a D- $\alpha$ -aminoacid  $NH_2-CR_{1b}(Cy)-COOH$  where the  $NH_2$  represents part of X-X.

25

26. A compound as claimed in Claim 1, which is selected from:  
 1-(Indole-6-carbonyl-D-phenylglyciny)-4-[2-(4-pyridinyl)-ethyl]piperazine;  
 1-(3-Chloroindole-6-carbonyl-D-phenylglyciny)-  
 30 4-[2-(4-pyridinyl)ethyl]piperazine;  
 1-(4-Methoxybenzoyl-D-phenylglyciny)-4-(1-methylpiperidin-4-

- 14 -

yl)piperazine;

1-(Indole-6-carbonyl-D-phenylglyciny1)-4-(1-methylpiperidin-4-yl)piperazine;

1-(4-Methoxybenzoyl-D-(2-chlorophenyl)glyciny1)-4-(1-methyl-  
5 piperidin-4-yl)piperazine;

1-(Indole-6-carbonyl-D-(2-chlorophenyl)glyciny1)-4-(1-methyl-  
piperidin-4-yl)piperazine; and

1-(4-Methoxybenzoyl-D-(2-trifluoromethylphenyl)glyciny1)-4-(1-  
methylpiperidin-4-yl)piperazine;

10 and physiologically-tolerable salts thereof.

27. (amended) A pharmaceutical composition, which comprises a  
compound as claimed in Claim 1 together with at least one  
pharmaceutically acceptable carrier or excipient.

15

28. (cancelled on national phase entry)

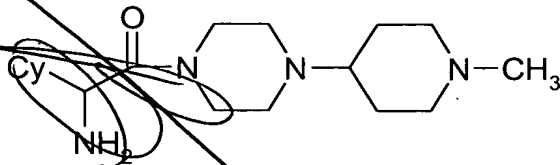
29. (cancelled on national phase entry)

20 30. A method of treatment of a human or non-human animal body  
to combat a thrombotic disorder, which comprises administering  
to said body an effective amount of a compound as claimed in  
claim 1.

25 31. (cancelled on national phase entry)

32. (cancelled on national phase entry)

33. (amended) A compound of the formula



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in which Cy is as defined in Claim 1, or a salt thereof.

34. (new) 1-(Indole-6-carbonyl-D-phenylglyciny1)-4-(1-  
methylpiperidin-4-yl)piperazine; or a physiologically-  
35 tolerable salt thereof.

- 15 -

*contd.**a<sup>8</sup>*

35. (new) A pharmaceutical composition, which comprises a compound as claimed in Claim 34 together with at least one pharmaceutically acceptable carrier or excipient.

*5*

36. (new) A method of treatment of a human or non-human animal body to combat a thrombotic disorder, which comprises administering to said body an effective amount of a compound as claimed in claim 34.

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